

, ATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 15 May 2001 (15.05.01)	To:
International application No. PCT/CA00/00948	Applicant's or agent's file reference 14226-4PCT
International filing date (day/month/year) 17 August 2000 (17.08.00)	Priority date (day/month/year) 19 August 1999 (19.08.99)
Applicant ALAOUI-JAMALI, Moulay, A. et al	

1. The designated Office is hereby notified of its election made:

 in the demand filed with the International Preliminary Examining Authority on:

12 March 2001 (12.03.01)

 in a notice effecting later election filed with the International Bureau on:2. The election was was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Claudio Borton Telephone No.: (41-22) 338.83.38
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PATENT COOPERATION TREATY

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:
 COTE, France
 Swabey Ogilvy Renault SWABEY OGILVY RENAULT
 Suite 1600 MCGILL COLLEGE
 1981 McGill College Avenue RECEIVED
 Montréal, Québec H3A 2Y3
 CANADA

MAR 13 2001

A.M. P.M.
 7 8 9 10 11 12 1 2 3 4 5 6

Date of mailing (day/month/year)
01 March 2001 (01.03.01)

Applicant's or agent's file reference	IMPORTANT NOTICE	
14226-4PCT		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/CA00/00948	17 August 2000 (17.08.00)	19 August 1999 (19.08.99)

Applicant	CENTRE FOR TRANSLATIONAL RESEARCH IN CANCER et al
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1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
 AU, KP, KR, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
 AE, AG, AL, AM, AP, AT, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EA, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on 01 March 2001 (01.03.01) under No. WO 01/14546

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer J. Zahra
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

SWABEY OGILVY RENAULT

MCGILL COLLEGE

RECEIVED

by fax and post

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

CÔTÉ, France et al.
SWABEY OGILVY RENAULT
1981 McGill College Avenue
Suite 1600
Montréal, Québec H3A 2Y3
CANADA

A.M.

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NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

FAX: 001 514 288 8389

Date of mailing
(day/month/year)

13.11.2001

Applicant's or agent's file reference
14226-4PCT FC

IMPORTANT NOTIFICATION

International application No.
PCT/CA00/00948

International filing date (day/month/year)
17/08/2000

Priority date (day/month/year)
19/08/1999

Applicant

CENTRE FOR TRANSLATIONAL RESEARCH IN CANCER et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer

MYLONAS, E

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ENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 14226-4PCT	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
International application No. PCT/CA 00/ 00948	International filing date (day/month/year) 17/08/2000	(Earliest) Priority Date (day/month/year) 19/08/1999
Applicant CENTRE FOR TRANSLATIONAL RESEARCH IN CANCER		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

contained in the international application in written form.

filed together with the international application in computer readable form.

furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. Certain claims were found unsearchable (See Box I).

3. **Unity of invention is lacking (see Box II).**

4. With regard to the title,

the text is approved as submitted by the applicant.
 the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

the text is approved as submitted by the applicant.

the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No. 1.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

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None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/00948

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12N15/12 C12N15/62 C07K14/47 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBL, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE EM_EST 'Online! EMBL; ID HS1272698, AC AA482412, 24 June 1997 (1997-06-24) HILLIER L ET AL.: "zt34d02.r1 Soares ovary tumor NbHOT Homo sapiens cDNA clone IMAGE:724227 5', mRNA sequence" XP002167205 98.5% nt seq identity with SEQ ID NO:1 in 495 nt overlap (14-506:60-554) the whole document</p> <p>---</p> <p style="text-align: center;">-/-</p>	1-5,10, 11



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

- °A° document defining the general state of the art which is not considered to be of particular relevance
- °E° earlier document but published on or after the international filing date
- °L° document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- °O° document referring to an oral disclosure, use, exhibition or other means
- °P° document published prior to the international filing date but later than the priority date claimed

- °T° later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- °X° document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- °Y° document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- °&° document member of the same patent family

Date of the actual completion of the international search

18 May 2001

Date of mailing of the international search report

08/06/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
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Authorized officer

van de Kamp, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 00/00948

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE EM_EST 'Online! EMBL; ID AA690874, AC AA690874, 19 December 1997 (1997-12-19) MARRA M ET AL.: "vt32d01.r1 Barstead mouse proximal colon MPLRB6 Mus musculus cDNA clone IMAGE:1164769 5', mRNA sequence" XP002167206 81.3% nt seq identity with SEQ ID NO:1 in 402 nt overlap (9-410:190-591) the whole document</p> <p>---</p>	1-5,10, 11
X	<p>WO 98 37901 A (BOEHRINGER INGELHEIM PHARMA ;MARLIN STEVEN D (US); TATAKE REVATI J) 3 September 1998 (1998-09-03) page 1, line 5-14 page 5, line 4-14 examples 1,2 claims 1,12,14 figures 1,2</p> <p>---</p>	8
X	<p>WO 98 00013 A (UNIV CALIFORNIA) 8 January 1998 (1998-01-08) page 2, line 7 -page 3, line 30 examples 1-8 claims 1,4,5</p> <p>---</p>	8
A	<p>NAGELHUS TA ET AL.: "A sequence in the N-terminal region of human uracil-DNA glycosylase with homology to XPA interacts with the C-terminal part of the 34-kDa subunit of replication protein A" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 10, 7 March 1997 (1997-03-07), pages 6561-6566, XP002167201 abstract</p> <p>---</p>	
A	<p>IFTODE C ET AL.: "Replication protein A (RPA): the eukaryotic SSB" CRITICAL REVIEWS IN BIOCHEMISTRY AND MOLECULAR BIOLOGY, vol. 34, no. 3, 1999, pages 141-180, XP001002021 abstract figure 1 page 159, left-hand column, line 34 -page 166, left-hand column, line 29; table 2</p> <p>---</p> <p>-/-</p>	

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 00/00948

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>WOLD MS: "Replication protein A: a heterotrimeric, single-stranded DNA-binding protein required for eukaryotic DNA metabolism" ANNUAL REVIEW OF BIOCHEMISTRY, vol. 66, 1997, pages 61-92, XP001002023 cited in the application abstract page 74, line 17 -page 76, line 27 ---</p>	
P, X	<p>DATABASE EM_HUM 'Online! EMBL; ID AC010271, AC AC010271, 17 September 1999 (1999-09-17) DOE JOINT GENOME INSTITUTE STANFORD HUMAN GENOME CENTER: "Homo sapiens chromosome 19 CTC-492K19, complete sequence" XP002167207 99.8% nt seq identity with SEQ ID NO:1 in 591 nt overlap (23191-23781:1-591) page 6-7 ---</p>	1, 2, 11
T	<p>CHO J M ET AL.: "RBT1, a novel transcriptional co-activator, binds the second subunit of Replication Protein A" NUCLEIC ACIDS RESEARCH, vol. 28, no. 18, 15 September 2000 (2000-09-15), pages 3478-3485, XP002167204 the whole document -----</p>	1-6, 11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 00/00948

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
WO 9837901	A	03-09-1998	AU	729063 B	25-01-2001
			AU	6672498 A	18-09-1998
			BR	9807622 A	15-02-2000
			CN	1249688 T	05-04-2000
			EP	0989853 A	05-04-2000
			HU	0002317 A	28-11-2000
			PL	335409 A	25-04-2000
			TR	9902068 T	21-12-1999
<hr/>			AU	3583797 A	21-01-1998
<hr/>			US	5976800 A	02-11-1999

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 00/00948**Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)**

On 4th line : insert before "transcriptional" the word "binding"

PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 14226-4PCT FC	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CA00/00948	International filing date (day/month/year) 17/08/2000	Priority date (day/month/year) 19/08/1999
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant CENTRE FOR TRANSLATIONAL RESEARCH IN CANCER et al.		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.		
2. This REPORT consists of a total of 10 sheets, including this cover sheet. <input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of 5 sheets.		
3. This report contains indications relating to the following items:		
I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input checked="" type="checkbox"/> Certain observations on the international application		

Date of submission of the demand 12/03/2001	Date of completion of this report 13.11.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Bladier, C Telephone No. +49 89 2399 7306



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA00/00948

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-10 as originally filed

Claims, No.:

1-11 as originally filed

Drawings, sheets:

1/1 as originally filed

Sequence listing part of the description, pages:

1-2, filed with the letter of 12.12.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA00/00948

the description, pages:

the claims, Nos.:

the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

the entire international application.

claims Nos. 7-9.

because:

the said international application, or the said claims Nos. 7-9 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

the written form has not been furnished or does not comply with the standard.

the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA00/00948

1. Statement

Novelty (N)	Yes: Claims 5, 6, 7, 10
	No: Claims 1-4, 8, 9, 11
Inventive step (IS)	Yes: Claims 5
	No: Claims 1-4, 6-11
Industrial applicability (IA)	Yes: Claims 1-6, 10, 11
	No: Claims

**2. Citations and explanations
see separate sheet**

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item I

Basis of the report

1. An amended set of **claims 1-9** has been filed with letter dated 16.10.2001.

Independent claim 1 has been modified to delete the unclear term 'identifying characteristics' and to adopt the formulation 'a gene encoding a protein *essentially* consisting in the amino acid sequence as set forth in SEQ ID N°2'. However, the introduction of the term '*essentially*' broadens the scope of amended claim 1 since it encompasses genes coding for proteins having an amino acid sequence different from SEQ ID N°2 *i.e.* proteins that might have a different function and hence that might be totally unrelated to the protein of the application. No basis can be found in the application as filed for such broadening. Hence amended claim 1 does not comply with the provisions of Article 34(2)(b) PCT. The same objection applies to claim 3 which recites 'a protein *essentially* consisting in the amino acid sequence set forth in SEQ ID N°2. Consequently, **amended claims 1 and 3** and claims which depend or refer to them (**amended claims 2, 4-9**) were ignored in the establishment of the present report, and the IPER was established on the basis of **claims 1-11** as originally filed (Rule 70.2(c) PCT).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

2. **Claims 7-9** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT) (see also Item V point 10).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

3. Reference is made to the following documents:

D1: Nagelhus T.A. *et al.*, JBC, 272(10), 7 March 1997, p6561-6566

D2: WO 98 37901 A, 3 September 1998

D3: WO 98 00013 A, 8 January 1998

D4: DATABASE EM_EST [Online] EMBL; ID HS1272698, AC AA482412, 24 June 1997, HILLIER L. *et al.*: 'zt34d02.r1 Soares ovary tumor NbHOT Homo sapiens cDNA clone IMAGE:724227 5', mRNA sequence'

D5: DATABASE EM_EST [Online] EMBL; ID AA690874, AC AA690874, 19 December 1997, MARRA M. *et al.*: 'vt32d01.r1 Barstead mouse proximal colon MPLRB6 Mus musculus cDNA clone IMAGE:1164769 5', mRNA sequence'

D6: Matsuda M. *et al.*, JBC, 270(8), 24 February 1995, p4152-4157

D7: Sharon L. *et al.*, Molecular and Cellular Biology, 18(7), July 1998, p4400-4406

Novelty - Article 33(2) PCT

4. Claim 1 recites 'a gene having the identifying characteristics of a replication protein A transcriptional activator 1 gene encoded by a nucleotide sequence as set forth in SEQ ID N°1.

This definition is totally unclear (see item VIII point 11), thereby rendering said gene indistinguishable from genes of the prior art. Indeed the formulation 'identifying characteristics' is vague as it does not characterize the gene in technical terms. Thus said 'identifying characteristics' can be interpreted as anything, for example as the ability to bind the second subunit of replication protein A (RPA). Consequently, the UNG gene which encodes a human uracil-DNA glycosylase able to bind the C-terminal part of the second RPA subunit (see document D1, abstract, Results 'Interaction between UNG and RPA2 in the two hybrid system') falls under this definition and anticipates the subject-matter of **claims 1-4** (Article 33(2) PCT).

5. The subject-matter of claim 8 is directed towards a method for inducing apoptosis of a targeted cell, said method comprising inserting into said cell a gene for apoptosis operably linked to a suitable promoter.

Documents D2 and D3 both disclose a method for inducing apoptosis of a targeted cell, said method comprising inserting into a cell a gene for apoptosis operably linked to a suitable promoter (D2, see claims 1, 12, 17, 19; D3, see claims 1, 5, 17, 18). Consequently documents D2 and D3 anticipate the subject-matter of **claim 8** (Article 33(2) PCT). In addition, they also anticipate the subject-matter of **claim 9** as the term 'RBT1' employed in claim 9 to characterize the promoter is an arbitrary designation meaningless to the skilled person (see Item VIII point 15).

6. The subject-matter of claim 11 is directed towards an antisense oligonucleotide hybridizing under stringent conditions to a mRNA encoding a RBT1 gene as set forth in SEQ ID N°1.

Document D4 and D5 disclose a human and mouse EST cDNA sequence showing 98.5% sequence identity with SEQ ID N°1 in 495 pb overlap and 81.3% sequence identity with SEQ ID N°1 in 402 pb overlap, respectively. Thus those documents anticipate the subject-matter of **claim 11**.

7. The subject-matter of **claims 5-7 and 10** is not found in the available prior art. Consequently, those claims are novel according to Article 33(2) PCT.

Inventive step - Article 33(3) PCT

8. Dependent claim 5 is directed towards a human protein interactor of the second RPA subunit (RPA32) having the amino acid sequence SEQ ID N°2.

Document D1 which is considered to represent the most relevant state of the art, also discloses a human protein interactor of RPA32. The subject-matter of claim 5 differs from D1 in that the protein interactor has a different amino acid sequence and is a transcriptional activator.

The technical problem to be solved by the present invention may therefore be regarded as finding an alternative RPA32 protein interactor able to promote transcription.

The solution to this problem provided by the application is the protein having the amino acid sequence SEQ ID N°2.

Although the prior art discloses RPA32 protein interactors (e.g. the DNA repair protein XPA and the protein RAD52, see documents D6 and D7), there is no indication to find the new one disclosed in the present application. Thus the IPEA is of the opinion that it would not be obvious for the person skilled in the art to find the above-mentioned RPA32 protein interactor. Consequently the subject-matter of dependent **claim 5** appears to involve an inventive step in the sense of Article 33(3) PCT.

9. **Claims 6, 7 and 10** do not meet the requirement of Article 33(3) PCT with respect to inventive step since the use of a gene for the preparation of a medicament for gene therapy, a method of gene therapy and the provision of an antibody raised against a gene are regarded as routine methods which would only be allowable in combination with a novel and inventive gene.

Industrial applicability - Articles 33(1) and (4) PCT

10. For the assessment of the present **claims 7-9** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

11. In **claim 1**, the subject-matter for which protection is sought is not clearly defined (Article 6 PCT). Firstly the wording 'a gene encoded by a nucleotide sequence' is meaningless. A nucleotide sequence encodes a protein, not a gene. Secondly the term 'having the identifying characteristics' is totally unclear and does not impose any limitation on the gene to which it refers as no technical characteristic is given.

Thus, said formulation broadens the scope and renders the gene of claim 1 indistinguishable from genes of the prior art (see novelty objection Item V point 4).

12. In **claim 1**, the formulation 'a replication protein A transcriptional activator' is not supported by the disclosure of the application. The description discloses that RBT1 binds RPA 32 kDa subunit (see page 5 lines 1-5, page 6 lines 6-23, page 8 lines 8-16), not that it activates RPA transcription. Furthermore the term 'gene' is not supported by the description since the description only discloses the isolation of human RBT1 cDNA. Consequently, an objection for lack of support is raised under Article 6 PCT.
13. In **claim 2**, the formulation 'a gene according to claim 2' is incorrect and should be 'a gene according to claim 1' (Article 6 PCT).
14. The clarity objection in claim 1 regarding the term 'having the identifying characteristics' is also raised for **claim 3** (Article 6 PCT).
15. The term 'RBT1' is an arbitrary designation used by the applicant to characterize the cDNA of the invention. Said term is not recognized in the prior art and thus is meaningless for the person skilled in the art. Consequently, **claim 9** referring to 'RBT1' lacks clarity (Article 6 PCT).
16. In claim 11, the wording 'a mRNA encoding a RBT1 gene' is meaningless. A mRNA sequence encodes a protein, not a gene. In addition, the formulation 'hybridizing under stringent conditions' is a functional definition that does not characterise the oligonucleotide in structural terms but by means of its effect. This mode of definition is vague since the conditions of hybridization are undefined (low, moderate, high stringency; temperature ?, % SDS?, % formamide?, % SSC?) and since the length of the mRNA fragment to which the antisense oligonucleotide hybridizes is not given. Thus this definition encompasses sequences which may be totally unrelated to the sequence of the invention. Consequently, the subject-matter of **claim 11** is not clearly defined (Article 6 PCT).
17. The term 'promoter' in **claims 6, 7 and 9** is not supported by the description since

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the application discloses that SEQ ID N°1 acts as a transcriptional activator and not that said sequence is a promoter. Consequently an objection for lack of support of said claims is raised (Article 6 PCT).

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(54) Title: REPLICATION PROTEIN A BINDING TRANSCRIPTIONAL FACTOR (RBT1) AND USES THEREOF

(57) Abstract: The present invention relates to replication protein A (RPA) transcriptional factors. There is provided a nucleotide sequence encoding a replication protein A binding transcriptional activator 1 (RBT1) and a protein encoded by such a nucleotide sequence. RBT1 has a high activity and is highly transactivated in cancer cells. The sequence may be used to treat neoplastic disorders and in gene therapy.

REPLICATION PROTEIN A BINDING TRANSCRIPTIONAL FACTOR
(RBT1) AND USES THEREOF

BACKGROUND OF THE INVENTION

5 (a) Field of the Invention

The invention relates to Replication Protein A (RPA) and more particularly to a RPA transcriptional factor to treat neoplastic disorders such as cancer.

10 (b) Description of Prior Art

Replication Protein A (RPA), also known as replication factor A (RFA), is a ubiquitous and abundant heterotrimeric protein required for DNA replication, repair and recombination in eukaryotes. 15 RPA nonspecifically binds single-stranded DNA and plays an essential role in the regulation of DNA metabolism via multiple protein interactions and/or RPA phosphorylation. More particularly, RPA binds single-stranded DNA with strong affinity (association constant of 10^9 - 10^{11} M $^{-1}$) and greatest affinity for polypyrimidine tracts. RPA also binds double-stranded DNA with lower affinity and is likely to facilitate DNA unwinding. RPA may play a role in the regulation of transcription by binding regulatory elements in promoters; in yeast, RPA 20 binds specific regulatory sequences in the promoters of DNA repair and metabolism genes (Singh K. et al., 1995, *Proceedings of the National Academy of Science USA* 92(11):4907-11).

RPA is made of three subunits: a 70-kDa subunit 30 (RPA70), a 32-kDa middle subunit (RPA32) and a 14-kDa subunit (RPA14). The RPA32 subunit is phosphorylated in a cell cycle-dependent manner.

RPA-protein interactions appear to be largely mediated by the large 70-kDa subunit (RPA70). RPA70 35 interacts with the p53, GAL4, VP16, EBNA1 and SV40T antigens and with DNA polymerase alpha (Wold, M., 1997,

5 Annual Review of Biochemistry, "Replication Protein A: A Heterotrimeric, Single-Stranded DNA-binding Protein Required for Eukaryotic DNA Metabolism"). It is also important in interaction with DNA repair proteins involved in damage recognition and excision.

10 Interaction with XPF stimulates its 5' junction-specific endonuclease activity, interaction with XPG targets this endonuclease to damaged DNA, and interaction with ERCC1 (ERCC1 also binds *xeroderma pigmentosum* group A factor, XPA, which is another NER factor) promotes exonuclease activity.

15 The possibility of interaction by the aforementioned repair proteins with RPA32 has not been clearly elucidated. However, interactions with some proteins involved in DNA repair appear to be mediated by RPA32, such as interaction with XPA and uracil-DNA glycosylase. A region of significant homology between uracil-DNA glycosylase and XPA was also reported, suggestive of the possibility of a common binding motif 20 to RPA32 across several different proteins. Furthermore, some important protein interactions, such as with RAD52, appear to involve all three subunits of RPA (Hays, S. et al., 1998, *Molecular and Cellular Biology* 18(7):4400-4406).

25 In cells, RPA is phosphorylated by DNA-dependent protein kinase (DNA-PK) when RPA is bound to single-strand DNA, during the S phase and after DNA damage; and also possibly by ATM.

30 Phosphorylation of RPA is observed in a cell-cycle dependent manner and in response to DNA damage (i.e. UV light, X-rays, cisplatin) in eukaryotic systems. This phosphorylation takes place predominantly on the N-terminal region of RPA32 and was previously thought to be effected by DNA-dependent protein kinase 35 (DNA-PK). However, RPA hyperphosphorylation still takes

place in SCID cells where DNA-PK is believed to be responsible for its repair and recombination defects. Ataxia telangiectasia mutated gene (ATM), an important cell cycle checkpoint protein kinase belonging to the 5 same kinase family as DNA-PK, may be responsible for the *in vivo* phosphorylation of RPA32. In *Saccharomyces cerevisiae*, the ATM homolog, MEC1, is essential for RPA phosphorylation. Furthermore, ionizing radiation-induced phosphorylation of RPA32 is deficient and 10 reduced in primary fibroblasts from patients suffering from ataxia telangiectasia in comparison to normal, aged fibroblasts.

The result of RPA32 phosphorylation on DNA metabolism is largely unsolved. It has been noted that 15 IR-induced RPA phosphorylation can be uncoupled from the S-phase checkpoint in ataxia telangiectasia cells, suggesting that RPA phosphorylation in itself is not necessary or sufficient for an S-phase arrest. Phosphorylation, however, may affect the conformation 20 of RPA, thereby modulating its affinity for DNA and its protein interactors, and altering the balance between DNA replication and repair. Hyperphosphorylation of RPA32 *in vivo* is concordant with a decrease in the binding of RPA to single-stranded DNA. This observation 25 is interesting to note since phosphorylated RPA32 is found predominantly in the S-phase of the cell cycle.

RPA has been found to have a high affinity for UV-damaged and cisplatin-damaged DNA and the accompanying phosphorylated form of RPA is correlated 30 strongly with a reduction of the *in vitro* DNA replication activity of the concerned cell extracts.

It would therefore be highly desirable to identify physiologically relevant protein interactors of the RPA32 subunit of Replication Protein A. 35 Identification of such protein interactors would

contribute to the understanding of DNA repair, transcription, and cell signaling. The proteins involved in nucleotide excision repair (NER), for example, are quite numerous and the basis for their 5 interaction and function is not yet completely understood. Understanding the regulation of these pathways would assuredly lend insight into their role in cancer susceptibility. RPA, as a protein involved integrally in modulating DNA repair, replication and 10 recombination, would be key to understanding the connection between and within pathways. The implications to cancer therapeutics and/or prevention would be significant.

15 **SUMMARY OF THE INVENTION**

One aim of the present invention is to provide a protein interactor of the RPA32 subunit of Replication Protein A (RPA).

Another aim of the present invention is to 20 provide a RPA transcriptional factor to treat neoplastic disorders such as cancer.

In accordance with the present invention, there is provided a gene having the characteristics of a gene encoded by a nucleotide sequence as set forth in Fig. 1 25 (SEQ ID NO:1).

The gene may be from a human, a mouse, a rat or a yeast.

In accordance with the present invention, there is also provided a protein having the identifying 30 characteristics of a protein encoded by a nucleotide sequence as set forth in Fig. 1 (SEQ ID NO:1).

The protein may be from a human, a mouse, a rat or a yeast.

Antibodies may be raised against the gene.

The gene, replication protein A binding transcriptional activator 1 (RBT1), encodes a protein interactor of the Replication Protein A (RPA). More particularly, a protein interactor of the Replication 5 Protein A 32KD subunit was identified. RBT1 binds RPA32.

The RBT1 gene has a high activity in cancer cells compared to normal cells, may be involved in carcinogenesis and is highly transactivated in cancer 10 cells.

The RBT1 nucleotide and/or amino acid sequences may be used to generate reagents, such as plasmids, antibodies and inhibitors, including antisense/antibodies which may be used in treating neoplastic 15 disorders such as cancer.

The RBT1 sequence of the present invention may also be used for the preparation of a medicament for gene therapy, wherein the RBT1 sequence is used as a specific promoter to overexpress genes of interest in 20 specific tissues.

In accordance with another embodiment of the present invention, there is provided a method of gene therapy, which comprises the use of RBT1 sequence as a promoter for overexpressing a gene in a suitable 25 tissue.

The RBT1 gene may further be used to induce apoptosis in cells such as cancerous cells, by modulating its expression using molecular or chemical approaches.

30 The RBT1 sequence of the present invention may also be used to develop antisenses and/or inhibitors to treat diseases including cancers and leukemia.

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 illustrates the nucleotide (SEQ ID NO:1) and the amino acid sequence (SEQ ID NO:2) of RBT1.

5 DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a gene sequence encoding a protein interactor of Replication Protein A, identified using the yeast two-hybrid system. The gene, named RPA 10 Binding Transcriptional Activator 1 (RBT1), has a putative open reading frame of 196 amino acids. The coding sequence of RBT1 corresponds to several expressed sequence tags (ESTs), including one derived from an ovary tumor cell line. The gene of the present 15 invention acts as a strong transcriptional activator in yeast and mammalian cells. Furthermore, transcriptional activation, as assayed by a luciferase reporter gene, demonstrated that the activity of the RBT1 gene of the present invention is higher in cancer cells compared to 20 normal non-immortalized cells. RBT1 expression is higher in cancer cells compared to normal cells. More particularly, a protein interactor of Human Replication 25 Protein A 32 (RPA32) was identified.

BLASTP homology searches against the deduced 25 amino acid sequence of RBT1 reveal that it is an undefined protein with little homology to known protein sequences. Further, BLASTN homology searches only identified approximately 20 human expressed sequence tags (ESTs) which had high homology to RBT1.

30 Northern blot using an RBT1 DNA probe showed one transcript of approximately 1.55 kb in size. *In silicio* analysis suggested that RBT1 consists of an open reading frame (ORF) of 196 amino acids and a theoretical molecular weight of 22 kDa. This is in 35 agreement with Western Blot analysis.

Differential expression of RBT1 was also investigated as it relates to cancer. Semi-quantitative analysis has shown that RBT1 is at least ten times more expressed in cell line H661 (cancer cells) than NHBEC 5 (normal cells).

Various cell lines are investigated to ascertain whether RBT1 has relevance to carcinogenesis. *In silicio* analysis also suggests that the N-terminal domain of RBT1 contains a putative DNA binding domain. 10 Whether RBT1 binds specific DNA regulatory elements is also being investigated.

The presence of an acidic domain in the C-terminal domain of RBT1 led to investigate whether RBT1 was a potential transcriptional activator. RBT1, fused 15 to the LexA binding domain, strongly promotes transcription of reporter genes LacZ and HIS3 in the yeast two-hybrid system, suggesting its possible role as a transcriptional activator.

RBT1 deletion constructs were designed to 20 determine the transactivating domain, and to define the domain which is essential for RPA32 interaction. The transactivation domain of RBT1 resides within 30 amino acids at the C-terminal. Truncation of RBT1 from the C-terminal end results in significant reduction of 25 transactivation of the reporter genes.

A mammalian transactivation assay confirmed that a GAL4-RBT1 fusion protein indeed acts as a strong transcriptional activator. Furthermore, transcriptional activation, as assayed by a luciferase reporter gene, 30 although high in all cancer cell lines examined, is at least 4 times higher in cell line MCF7. Transactivation studies were also performed using a mammalian system to verify that RBT1 acts as a transcriptional activator in its native cellular environment. RBT1, fused to a GAL4 35 DNA binding domain, strongly promotes transcription of

the luciferase reporter gene. This transactivation was strongly attenuated by truncation of the gene from the C-terminal end. Further, the relative transactivation of the luciferase reporter by the full length RBT1 gave 5 values higher than the positive control construct, TLS, in cell lines 293, MDA231, MCF7 and Saos-2, suggesting a possible role in cancer.

RBT1 binds RPA32 in the yeast two-hybrid system. Truncation of RBT1 suggests that the domain of RBT1 10 responsible for binding to RPA32 resides between amino acid 1-120. This region also contains a putative DNA binding domain which needs to be clarified. A GST-RBT1 construct was found to bind *in vitro* translated RPA32. A GFP-RBT1 was transfected into cell line 293 and shown 15 to localize in the nucleus in a pattern similar to, and possibly overlapping with, that of RPA32.

RPA32 was amplified from MCF7 cDNA and cloned, in frame, into pBTM116, a LexA two-hybrid plasmid subsequently referred to as RPA34-pBTM116. This plasmid 20 construct was transformed into yeast strain L40 (MAT α trp1 leu2 his3 URA3:(lexAop)8-lacZ LYS2::(lexAop)4-HIS3 lys2 ura3 ade2 gal80 gal4) prior to library transformation. Transcription of the HIS3 reporter gene was found to occur in the absence of protein- 25 protein interaction; this was attributed to potential transactivation function of RPA32. To reduce background, 3-aminotriazole (3-AT), a metabolic inhibitor, was included in media lacking histidine to increase the stringency of the screen. A human 30 osteosarcoma GAL4 cDNA library was amplified according to CLONTECH recommended protocols.

400,000 colonies were screened and 72 colonies were identified which were able to grow on media lacking histidine and containing 25 mM 3-AT. These 35 colonies were restreaked on the same media and

replicated to media containing X-gal. Based on growth rates on SC-histidine (25 mM 3-AT) media and on level of induction of the B-gal reporter gene, positive colonies were classified into three groups, strong, 5 intermediate, and weak interactors. All colonies which demonstrated high levels of induction of the B-gal reporter gene were assayed by PCR using a primer specific to RPA14 and ADC1, a sequence in the terminator region of the library plasmid. Interacting 10 plasmids from several of these colonies were purified and sequenced. Both PCR and sequencing experiments showed that the strongest interactors were representative of RPA32.

A putative positive identified as a RPA32 interacting protein was sequenced and found to have no strong homology to known proteins. This gene, referred to as RBT1, was subcloned from the pACT2 vector into pBTM116 for purposes of mini-screening the two-hybrid library. However, the library could not be screened 20 using RBT1-pBTM116 as bait because of extremely strong transactivation of the yeast reporter genes by itself. This observation suggests that RBT1 may be a transcriptional activator. Although some proteins fortuitously show transcriptional transactivation, its 25 binding to RPA32 supports the notion that RBT1 may not be among such proteins. Experiments were done in attempts to ascertain whether RBT1 functions as a transcriptional activator.

There are several dbEST matches for RBT1 in 30 GenBank. Two representative full length clones have been obtained, DNA was purified, and may be sequenced completely.

Plasmid constructs with truncations at the 3' end of RBT1 have been cloned and transformed into yeast 35 strain L40. ONPG assays shows substantial diminishment

of B-gal activity with just 60 bp deleted from the 3', suggesting that the potential transcriptional activation domain of RBT1 lies at the carboxy terminal.

Similar constructs may be cloned into a vector 5 for transfection into human cells, using an in-frame fusion to GAL4 DNA-binding domain and utilizing a second plasmid bearing a luciferase reporter gene under the control of several GAL4 binding sites. These experiments determine whether the transactivation found 10 in the yeast system are physiologically relevant.

RBT1 may be overexpressed in various human cell lines to ascertain possible phenotypic effects. Experiments may include UV and chemical challenge.

Antibodies against RBT1 may be raised for 15 subsequent protein localization experiments in human cells. This antibody may also be used for various co-immunoprecipitation experiments to show RPA-RBT1 binding.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and 25 including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended 30 claims.

WHAT IS CLAIMED IS:

1. A gene having the identifying characteristics of a replication protein A transcriptional activator 1 (RBT1) gene encoded by a nucleotide sequence as set forth in SEQ ID NO:1.
2. A gene according to claim 2, said gene being from a species selected from the group consisting of human, mouse, rat and yeast.
3. A protein having the identifying characteristics of a protein encoded by a nucleotide sequence as set forth in SEQ ID NO:1.
4. A protein according to claim 3, said protein being from a species selected from the group consisting of human, mouse, rat and yeast.
5. A protein according to claim 4, said protein consists in the amino acid sequence set forth in SEQ ID NO:2.
6. Use of a gene according to claim 1 for the preparation of a medicament for gene therapy, wherein said gene is used as a promoter for overexpressing a gene in a suitable tissue.
7. A method of gene therapy, which comprises the use of a gene according to claim 1 as a promoter for overexpressing a gene in a suitable tissue.
8. A method for inducing apoptosis of a targeted cell, said method comprising inserting into said cell

a gene for apoptosis operably linked to a suitable promoter.

9. A method according to claim 8, wherein said promoter consists of a RBT1 gene promoter.

10. An antibody raised against a gene according to claim 1.

11. An antisense oligonucleotide hybridizing under stringent conditions to a mRNA encoding a RBT1 gene as set forth in SEQ ID NO:1.